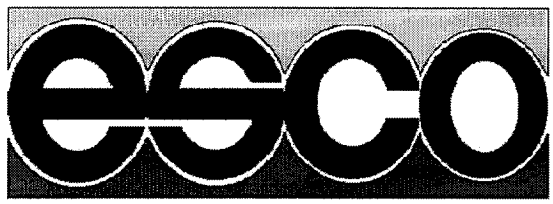
201-14878A



Chemicals for the Information Age

EPA HPV Challenge
Keto Acid Category Test Plan - Revised

ESCO Company Limited Partnership
2340 Roberts Street
Muskegon, Michigan 49443

The Keto Acid Category

Keto Acid Name	Chemical Name	C.A.S. Number
EtKeto Acid	Benzoic acid, 2-[4-(diethylamino)-2-hydroxybenzoyl]	5809-23-4
BuKeto Acid	Benzoic acid, 2-[4-(dibutylamino)-2-hydroxybenzoyl]	54574-82-2

Category Definition

1. Identification of Category Members

The EPA High Production Volume (HPV) Challenge identified the following chemical as a high production volume chemical:

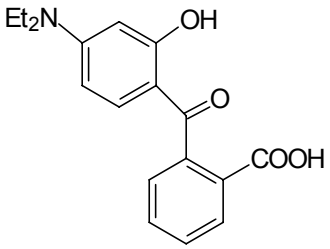
Keto Acid Name	Chemical Name	C.A.S. Number
EtKeto Acid	Benzoic acid, 2-[4-(diethylamino)-2-hydroxybenzoyl]	5809-23-4

The EPA guidance document on the development of chemical categories defines a category as "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. The similarity may be based on a common functional group."

The following chemical is very similar to EtKeto Acid in molecular structure:

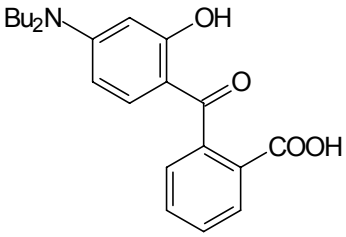
Keto Acid Name	Chemical Name	C.A.S. Number
BuKeto Acid	Benzoic acid, 2-[4-(dibutylamino)-2-hydroxybenzoyl]	54574-82-2

BuKeto Acid is not identified by the EPA as an HPV chemical, but the structure and the physiochemical and toxicological properties are so similar to EtKeto Acid that it is being included with EtKeto Acid in the keto acid category. The chemical structure diagrams of these two keto acids are shown below.



ETKETO

Formula: $C_{18}H_{19}NO$
MW: 313



BUKETO

Formula: $C_{22}H_{27}NO_4$
MW: 369

2. Category Analysis

The keto acid category members have closely related chemical structures. The keto acids in this category are weak acids with the only differences in the stuctures being the functional group on the nitrogen. EtKeto Acid has basically the same structure as

BuKeto Acid, except the ethyl group attached to the nitrogen is replaced with a butyl group on BuKeto Acid.

3. Test Plan Matrix

The keto acid category test plan matrix that is shown in Table 1 was developed after a review of the existing data available. The matrix is arranged by category members in columns and the screening data endpoints in rows. The table indicates how data are provided for each endpoint.

4. Test Plan Rationale

For each of the screening data endpoints, including physical and chemical data, environmental fate and pathways, ecotoxicity, and toxicologoical data, the rationale for using the category approach is included in the following discussion.

Table 1: Test Plan Matrix for the Keto Acid Category

Screening Endpoints	EtKeto Acid (5809-23-4)	BuKeto Acid (54574-82-2)
Physical and Chemical Data		
Melting Point	A	A
Boiling Point	A	A
Density (Specific Gravity)	A	A
Vapor Pressure	A	A
Partition Coefficient (n-Octanol/Water)	A	A
Water Solubility	A	A
pH Value and pKa Value	C	A
Environmental Fate and Pathways		
Photodegradation	A	A
Stability in Water (Hydrolysis)	NA	NA
Transportation and Distribution between Environmental Compartments	A	A
Biodegradation	C	A
Ecotoxicity		
Acute Toxicity to Fish	C	A
Acute Toxicity to Aquatic Invertebrates	C	A
Toxicity to Aquatic Plants (e.g. Algae)	C	A
Toxicological Data		
Acute Oral Toxicity	C	A
Acute Dermal Toxicity	C	A
Repeated Dose Toxicity	C	A
Gene mutation	C	A
Genetic Toxicity – Chromosomal Aberrations	C	A
Toxicity to Reproduction	C	A
Developmental Toxicity/Teratogenicity	C	A^1

Key: A = Endpoint fulfilled with data
A^1 = Endpoint fulfilled by Toxicity to Reproduction Test data
C = Endpoint fulfilled by other category members data
NA = Test not applicable

4.1 Physical and Chemcial Data

Listed in Table 2 are the values for the physical and chemical data endpoints for the keto acid category. All of the data listed can be found in the robust summaries for the keto acid category. The boiling points were estimated using the EPIWin model. The vapor pressures were also estimated by the EPIWin model. The partition coefficient was measured for BuKeto Acid using OECD Guideline 107. The partition coefficient was estimated for EtKeto Acid using Advanced Chemistry Development Software as reported by the American Chemistry Society registry. The estimated values using this model for BuKeto Acid closely matched the measured values. We expect that because the estimated partition coefficients match the measured values for BuKeto, the estimated values for EtKeto Acid would be reliable because of the close structural similarity to BuKeto Acid. The water solubility of BuKeto Acid was measured and found to be very limited. The water solubility of EtKeto Acid was estimated using Advanced Chemistry Development Software as reported by the American Chemistry Society registry. The solubility increases with increased pH. Because the pKa value could not be calculated due to limited solubility for BuKeto Acid in water, EtKeto Acid would be expected to have similar results because of limited solubility. No further physical and chemical tests are planned for the keto acid category.

Table 2: Physical and Chemical Data

Screening Endpoints	EtKeto Acid (5809-23-4)	BuKeto Acid (54574-82-2)
Physical and Chemical Data		
Melting Point	201 - 204ºC	184ºC
Boiling Point	480ºC	526ºC
Density (Specific Gravity)	1.179 g/ml	1.179 g/ml
Vapor Pressure	1.76×10^{-10} at 25°C	1.47×10^{-11} at 25°C
Partition Coefficient (n-Octanol/Water)	Log D = 3.18 at pH 4.0 Log D = 0.42 at pH 7.0 Log D = -0.27 at pH 8.0	Log P_{ow} > 5.003 at pH 5.0 Log P_{ow} = 2.670 at pH 7.0 Log P_{ow} = 1.645 at pH 9.0
Water Solubility	Sparingly soluble at pH 4.0 Slightly soluble at pH 7.0 Soluble at pH 8.0 All estimated at 25°C	0.000137 kg/M^3 at 30°C and pH 5.0 0.0298 kg/M^3 at 30°C and pH 7.0 1.645 kg/M^3 at 30°C and pH 9.0
pH Value and pKa Value		Not soluble in water enough to perform the test

4.2 Environmental Fate and Pathways

Listed in Table 3 are the values for the environmental fate and pathway endpoints for the keto acid category. All of the data listed can be found in the robust summaries for

the keto acid category. The photodegradation and hydrolysis endpoints for the keto acids were estimated with the EPA model, EPIWin. Because the keto acids are solids, the photodegradation pathway is not a very likely scenario for degradation. Very little of the keto acids dissolve in water, so hydrolysis is also not a very likely route of degradation. Hydrolysis is unlikely because the molecules contain no hydrolyzable functions. The most likely route is adsorption to the soil and biodegradation. The biodegradation results from testing Buketo Acid shows that it is not readily biodegradable, which confirms the model results. Because EtKeto Acid is so similar to BuKeto Acid structurally, we would expect that EtKeto is not readily biodegradable either. The EPIWin Model predicts that EtKeto Acid would not be readily biodegradable. Another test that confirmed the information from the modeling is the adsorption/desorption to soil on BuKeto Acid. BuKeto Acid was strongly absorbed on to the soils tested, and it did not readily desorb from the soils. This result is consistent with the EPWin modeling information. Because EtKeto is structurally similar to BuKeto, it is expected that EtKeto Acid would have similar biodegradation results, and because all of the other endpoints have adequate data, no further environmental fate and pathways tests or estimations are planned for the keto acid category.

Table 3: Environmental Fate and Pathways

Screening Endpoints	EtKeto Acid (5809-23-4)	BuKeto Acid (54574-82-2)
Environmental Fate and Pathways		
Photodegradation	EPIWin Model Half-life ($t^{1/2}$) = 0.05 days	EPIWin Model Half-life ($t^{1/2}$) = 0.05 days
Stability in Water (Hydrolysis)	EPIWin Model Half-life ($t^{1/2}$) = 38 days	EPIWin Model Half-life ($t^{1/2}$) = 15 days
Transportation and Distribution between Environmental Compartments	EPIWin Model Air: 0.0002% Water:19.9% Soil: 78.4% Sediment: 1.74% Persistence: 44 days	EPIWin Model Air: 0.02% Water:30.2% Soil: 69.6% Sediment: 0.2% Persistence: 18 days
Biodegradation		BuKeto Acid did not biodegrade during the 28 day study.

4.4 Ecotoxicity

Listed in Table 4 are the values for the ecotoxicity endpoints for the keto acid category. All of the data listed can be found in the robust summaries for the keto acid category. The data provided for BuKeto Acid shows some toxicity to fish within its solubility range and some inhibition to alga growth within its solubility range. EtKeto Acid, based on its similar chemical structure is expected to show some toxicity to fish and some inhibition

to alga growth. Some further tests that were completed on BuKeto Acid include a prolonged toxicity study on rainbow trout, a respiration inhibition test on activated sludge, a toxicity study of BuKeto Acid on earthworms, and a toxicity test of BuKeto Acid on the growth of higher plants. The prolonged toxicity to rainbow trout confirmed the toxicity of BuKeto Acid to fish. The BuKeto Acid earthworm study, respiration inhibition test, and the higher plant growth study showed no adverse effects on the earthworm, the activated sludge or the growth of plants from BuKeto Acid. Because EtKeto is structurally similar to BuKeto, it is expected that EtKeto Acid would have similar results, so no further ecotoxicity testing is planned for the keto acid category.

Table 4: Ecotoxicity

Screening Endpoints	EtKeto Acid (5809-23-4)	BuKeto Acid (54574-82-2)
Ecotoxicity		
Acute Toxicity to Fish		96 h LC_{50} = 16.3 p.p.m.
Acute Toxicity to Aquatic Invertebrates		24 h EC_{50} value = 65.8 p.p.m. 48 h EC_{50} value = 36.3 p.p.m.
Toxicity to Aquatic Plants (e.g. Algae)		EC_{50} = 25.73 p.p.m.

4.5 Toxicological Data

Listed in Table 5 are the values for the toxicological endpoints for the keto acid category. All of the data listed can be found in the robust summaries for the keto acid category. Acute oral toxicity results are included for both the keto acids. In addition to dermal toxicity, BuKeto Acid was also tested for skin irritation (rabbit), eye irritation (rabbit), and skin sensitization (guinea pig). EtKeto Acid was also tested for skin irritation (rabbit). All of these tests show the keto acids in this category show little or no irritation to the skin or eyes or sensitization to the skin. The repeated dose result for BuKeto Acid shows some toxicity at the medium and greatest dose tested. The *In vivo* gene mutation tests (*In Vivo* Rat Liver Unscheduled DNA Synthesis Assay) on BuKeto Acid was negative even though BuKeto Acid was clastogenic *in vitro* when tested for such effects, to toxic concentrations, in the presence of S9 mix with an established Chinese hamster ovary (CHO) cell line. The gene mutation test for BuKeto Acid was negative. The reproduction test on BuKeto Acid was based on the OECD Method 415, which showed some signs of toxicity including a moderate reduction in body weight gain with a concomitant slight reduction in food consumption at 1000 mg/kg/day in males only. There were no notable effects seen in 50 mg/kg/day or 250 mg/kg/day in males or at any dose level in females. The reproduction test was carried on for 10 weeks prior to mating and carried through to 21 days post partum. Based on the results of this test no further developmental tests were conducted. Because of the structural similarity of EtKeto to BuKeto, it is expected that EtKeto would have similar toxicological results, so no further toxicological testing is planned for the keto acid category.

Table 5: Toxicological Data

Screening Endpoints	EtKeto Acid (5809-23-4)	BuKeto Acid (54574-82-2)
Toxicological Data		
Acute Oral Toxicity	LD_{50} > 5.0 g/kg	LD_{50} > 5.0 g/kg
Acute Dermal Toxicity		LD_{50} > 2.0 g/kg
Repeated Dose Toxicity		NOEL > 250 mg/kg/day in males NOEL > 1000 mg/kg/day in females
Gene mutation		Negative
Genetic Toxicity – Chromosomal Aberrations		"In the presence of S9 mix BuKeto Acid was a potent inducer of chromosomal aberrations when tested at toxic concentrations of 20 and 30 µg/ml. This response was dose related. There was no evidence that BuKeto Acid induced chromosomal aberrations in the absence of the S9 mix."
Genetic Toxicity – In Vivo		Negative
Toxicity to Reproduction		NOEL = 50 mg/kg/day
Developmental Toxicity/Teratogenicity		NOEL = 50 mg/kg/day

5. Test Plan Conclusion

EtKeto Acid and BuKeto Acid have closely related chemical structures. The keto acids in this category are weak acids with the only differences in the stuctures being the functional group on the nitrogen. EtKeto Acid is basically the same as BuKeto Acid, except the ethyl group attached to the nitrogen is replaced with a butyl group on BuKeto Acid. All of the data from the robust summaries for the keto acid category show a similar pattern of physical and chemical properties, and a similar pattern of effects from environmental fate data. Ecotoxicity data, and toxicological data are provided for BuKeto Acid and because of the structural similarity of EtKeto to BuKeto, it is expected that EtKeto would have similar ecological and toxicological results.

The data provided in the robust summaries show a pattern that is consistent with the close molecular structure of the keto acids in this category. Both EtKeto Acid and BuKeto Acid are intermediates used in the production of color formers.

The data help confirm the validity of the category. No further new testing is planned for the keto acid category.